The specification has been further amended to correct SEQ ID NO: 11 in the sequence listing. Support for the amendment to SEQ ID NO: 11 can be found in Figure 2 of the specification. The corrected sequence listing is submitted to comply with the requirements of 37 C.F.R. §1.825 (a) and (b).

Claims 1, 2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34, 35, 38, 40-42 are amended herein. Claims 3, 5, 7-9, 14, 16, 18, 20, 25, 27, 29, 31-33, 36, 37, 39 and 43-47 are canceled herein, without prejudice to renewal. Claims 1, 11, 23, 34, and 40-42 are amended to correct form. Claims 15, 17, 19, 21, 22, 26, 28, and 30 are amended to correct dependency. Claim 35 is amended to place it in dependent form. New claims 48-69 are added herein.

Support for the amendment of claims 1, 11, 23, and 34 can be found in the specification at page 3, lines 6-12; page 10, lines 24-25 and 30-33; page 11 lines 20-25. Additional support for the amendment of claim 1 can be found in the specification at page 19, lines 3-9. Additional support for the amendment of claim 11 can be found in the specification at page 30, lines 9-10. Additional support for the amendment of claim 23 can be found in the specification at page 29, lines 30-31 and in Figure 2. Additional support for the amendment of claim 34 can be found in the specification at page 29, lines 26-27 and 30-33, and in Figure 2.

Support for the amendment of claims 2, 4, 6, 26, 28, and 30 can be found in the specification at page 19, lines 5-9. Support for the amendment of claim 10 can be found in the specification at page 10, lines 24-28. Support for the amendment of claims 12, 21, and 22 can be found in the specification at page 30, lines 9-10 and in Figure 2. Support for the amendment of claim 13 can be found in the specification at page 29, lines 30-31, page 34, lines 14-16 and in Figure 2. Support for the amendment of claims 14, 15, 17, and 19 can be found in the specification at page 30, lines 18-20. Support for the amendment of claim 24 can be found in the specification at page 30, lines 9-10; page 34 lines 14-16; and in Figure 2. Support for the amendment of claim 35 can be found in the specification at page 29, lines 26-27 and in Figure 2. Support for the amendment of claims 38 and 42 can be found in the specification at page 17, lines 27-35, and in original claims 38 and 39.

Support for new claims 48-50, 52, 54-56, 58, and 63-65 can be found in the sequence listing. Support for new claims 51, 59-62, and 68 can be found in the specification at page 30, lines 9-10 and in Figure 2. Support for new claims 53 and 57 can be found in the specification at page 10, lines 24-28. Support for new claims 66 and 67 can be found in the specification at page 29, lines 26-27 and in Figure 2. Support for new claim 69 can be found in the specification at page 18, lines 13-16.

No new matter is added by any of the foregoing amendments. Examination of the subject application is respectfully requested.

Restriction Requirement

Applicants elect with traverse Examiner's Group I (claims 1-35, and 38-41), drawn to an antibody. Applicants submit that the subject matter of Group III (claim 42), drawn to a method of treatment, should be classified in the same group as the claims in Group I. Applicants submit that it is not an undue burden on the Examiner to include the subject matter of claim 42 with the subject matter of the claims in Group I. Reconsideration of the restriction requirement is respectfully requested.

Conclusion

If any minor matters remain to be addressed prior to examination, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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Marked-up Version of Amended Claims
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

In the specification:

Please replace the paragraph at page 13, lines 11-14 with the following:

H-CDR1 of CC49 and 21/28'CL differ at three positions, 31, 32, and 34. However, SDR variants which include a corresponding human residue at positions 32 and [24] 34 demonstrate no antigen binding affinity. Thus, a functional SDR variant should not include a corresponding human residue at either of these positions.

Please replace the paragraph at page 15, lines 11-13 with the following:

H-CDR1 of CC49 and 21/28'CL differ at three positions, 31, 32, and 34. SDR variants which include a corresponding human residue[s] at positions 32 and [24] 34 demonstrate no antigen binding affinity.

Please replace the paragraph at page 29, lines 11-16 with the following:

H-CDR1 of CC49 and 21/28'CL differ at three positions, 31, 32, and 34. The residue at position 31 is directly involved in ligand binding in 12 of the 31 complexes; in five of those, only main chain atoms were involved. The residue at position 32 is ligand contacting in eight of the 31 complexes of known structure. The residue at position 34 is involved in ligand contact in none of the 31 complexes of known structure. Residues at positions 32 and [24] 34 of the CC49 H-CDR1 were replaced with the corresponding residues of 21/28'CL MAb (^{32,34}H) to test whether positions 32 is important for ligand contact and in eliciting anti-idiotypic response.

Please replace the paragraph at page 30, lines 7-8 with the following:

Variant ^{32,34}H: residues at positions 32 and [24] 34 of the CC49 H-CDR1 were replaced with the corresponding residues of 21/28'CL MAb.

Please replace the paragraph at page 30, lines 9-10 with the following:

Variant $^{60\text{-}62,\ 64}$H: residues at positions 60, 61, 62 and 64 of the CC49[H-CDR1] H-CDR2 were replaced with the corresponding residues of 21/28'CL MAb.

In the claims:

1. (Once amended) A humanized anti-TAG-72 CC49 antibody comprising:

a light chain Complementarity Determining Region (L-CDR)1 [Regions (L-CDRs), comprising L-CDR1], a L-CDR2, and a L-CDR3; and a heavy chain Complementarity Determining Region (H-CDR)1 [Regions (H-CDRs), comprising H-CDR1], a H-CDR2, and a H-CDR3,

wherein L-CDR3, H-CDR1, H-CDR2 and H-CDR3 [are from a] comprise murine monoclonal CC49 [non-human] antibody Complementarity Determining Regions (CDRs) and at least one of L-CDR1 and L-CDR2 [are] comprises a human monoclonal LEN antibody Complementarity Determining Region (CDR) [sequences],

wherein the humanized CC49 antibody retains binding affinity for TAG-72 and has reduced immunogenicity, as compared to a parental humanized CC49 antibody.

2. (Once amended) The humanized antibody of claim 1, wherein L-CDR1 [is from] comprises the [a] human monoclonal LEN antibody CDR.

3. (Canceled) [The humanized antibody of claim 2, wherein L-CDR1 is from human monoclonal antibody LEN.]

4. (Once amended) The humanized antibody of claim 1, wherein L-CDR2 [from] comprises the [a] human monoclonal LEN antibody CDR.

5. (Canceled) [The humanized antibody of claim 4, wherein L-CDR2 is from human monoclonal antibody LEN.]

6. (Once amended) The humanized antibody of claim 1, wherein both L-CDR1 and L-CDR2 [are] comprise human monoclonal LEN antibody CDRs [sequences].

7. (Canceled) [The humanized antibody of claim 1, wherein L-CDR1 and L-CDR2 are human antibody sequences from the same human antibody.]

8. (Canceled) [The humanized antibody of claim 7, wherein L-CDR1 and L-CDR2 are human antibody sequences from human monoclonal antibody LEN.]

9. (Canceled) [The humanized antibody of claim 6, wherein L-CDR1 and L-CDR2 are human antibody sequences from different human antibodies.]

10. (Once amended) The humanized antibody of claim 1, wherein the parental humanized CC49 antibody comprises three light chain hypervariable regions and three heavy chain hypervariable regions [L-CDR3, H-CDR1, H-CDR2, and H-CDR3 are from] of the murine monoclonal CC49 antibody [CC49], a variable light chain framework of a human monoclonal LEN antibody, and a variable heavy chain framework of a human monoclonal 21/28'CL antibody.

11. (Once amended) A humanized anti-TAG-72 CC49 antibody comprising:

a light chain Complementarity Determining Region (L-CDR)1 [Regions (L-CDRs), comprising L-CDR1], a L-CDR2, and a L-CDR3; and a heavy chain Complementarity Determining Region (H-CDR)1 [Regions (H-CDRs), comprising H-CDR1], a H-CDR2, and a H-CDR3,

wherein at least L-CDR3, H-CDR1, H-CDR2 and H-CDR3 comprise murine CC49 monoclonal antibody Complementarity Determining Regions (CDRs) and wherein at least one amino acid [of] at position[s] 60, 61, 62, or 64 in the murine CC49 H-CDR2 is replaced with [a] an amino acid at a corresponding position in [amino acid from a] the human monoclonal 21/28'CL antibody,

wherein the humanized CC49 antibody retains binding affinity for TAG-72 and has reduced immunogenicity, when compared to a parental humanized CC49 antibody.

12. (Once amended) The humanized antibody of claim 11, wherein [the] an asparagine at position 60 in the murine CC49 H-CDR2 is replaced with a serine [human antibody is 21/28'CL].

13. (Once amended) The humanized antibody of claim 11, wherein [the] a threonine [amino acid] at position 97 of the murine CC49 L-CDR3 is replaced with a serine [corresponding amino acid from a human antibody].

14. (Canceled) [The humanized antibody of claim 11, wherein at least one of L-CDR1 and L-CDR2 are human antibody sequences.]

15. (Once amended) The humanized antibody of claim [14] 11, wherein L-CDR1 [is] comprises a human monoclonal LEN antibody Complementarity Determining Region (CDR) [sequence].

16. (Canceled) [The humanized antibody of claim 15, wherein L-CDR1 is from human monoclonal antibody LEN.]

17. (Once amended) The humanized antibody of claim [14] 11, wherein L-CDR2 [is] comprises a human monoclonal LEN antibody CDR [sequence].

18. (Canceled) [The humanized antibody of claim 17, wherein L-CDR2 is from human monoclonal antibody LEN.]

19. (Once amended) The humanized antibody of claim [17] 11, wherein both L-CDR1 and L-CDR2 [are] comprise human monoclonal LEN antibody Complementarity Determining Regions [sequences].

20. (Canceled) [The humanized antibody of claim 19, wherein L-CDR1 and L-CDR2 are human antibody sequences from the same human antibody.]

21. (Once amended) The humanized antibody of claim [20] 11, wherein [L-CDR1 and L-CDR2] a glutamic acid at position 61 in the murine CC49 H-CDR2 is replaced with a glutamine [are from human monoclonal antibody LEN].

22. (Once amended) The humanized antibody of claim [19] 11, wherein [L-CDR1 and L-CDR2] an arginine at position 62 in the murine CC49 H-CDR2 is replaced with a lysine [are human antibody sequences from different human antibodies].

23. (Once amended) A humanized anti-TAG-72 CC49 antibody comprising:

a light chain Complementarity Determining Region (L-CDR)1 [Regions (L-CDRs), comprising L-CDR1], a L-CDR2, and a L-CDR3; and a heavy chain Complementarity Determining Region (H-CDR)1 [Regions [(H-CDRs), comprising H-CDR1], a H-CDR2, and a H-CDR3,

wherein at least L-CDR3, H-CDR1, H-CDR2 and H-CDR3 comprise murine CC49 monoclonal antibody Complementarity Determining Regions (CDRs), and wherein [an amino acid] a threonine at position 97 [of] in the murine CC49 L-CDR3 is replaced with a [corresponding amino acid from a human antibody] serine,

wherein the humanized CC49 antibody retains binding affinity for TAG-72 and has reduced immunogenicity, when compared to a parental humanized CC49 antibody.

24. (Once amended) The humanized antibody of claim 23, wherein at least one amino acid of positions 60, 61, 62, or 64 in the murine CC49 H-CDR2 is replaced with [a] an amino acid at a corresponding position in [amino acid from a] the human monoclonal 21/28'CL antibody.

25. (Canceled) The humanized antibody of claim 23, wherein at least one of L-CDR1 and L-CDR2 are human antibody sequences.]

26. (Once amended) The humanized antibody of claim [25] 23, wherein L-CDR1 [is] comprises a human monoclonal LEN antibody Complementarity Determining Region (CDR) [sequence].

27. (Canceled) [The humanized antibody of claim 26, wherein L-CDR1 is from human monoclonal antibody LEN.]

28. (Once amended) The humanized antibody of claim [25] 23, wherein L-CDR2 [is] comprises a human monoclonal LEN antibody CDR [sequence].

29. (Canceled) [The humanized antibody of claim 28, wherein L-CDR2 is from human monoclonal antibody LEN.]

30. (Once amended) The humanized antibody of claim [25] 23, wherein both L-CDR1 and L-CDR2 [are from] comprise human monoclonal LEN antibody Complementarity Determining Regions [sequences].

31. (Canceled) [The humanized antibody of claim 30, wherein L-CDR1 and L-CDR2 are human antibody sequences from the same human antibody.]

32. (Canceled) [The humanized antibody of claim 31, wherein L-CDR1 and L-CDR2 are from human antibody sequences from human monoclonal antibody LEN.]

33. (Canceled) [The humanized antibody of claim 30, wherein L-CDR1 and L-CDR2 are human antibody sequences from different human antibodies.]

34. (Once amended) A humanized anti-TAG-72 CC49 antibody comprising:

a light chain Complementarity Determining Region (L-CDR)1 [Regions (L-CDRs), comprising L-CDR1], a L-CDR2, and a L-CDR3 ; and a heavy chain Complementarity Determining (H-CDR)1 [Regions (H-CDRs), comprising H-CDR1], a H-CDR2, and a H-CDR3,

wherein L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2 and H-CDR3 are of a murine CC49 antibody, and

wherein (1) a threonine is [residues] at position[s] 94 in the L-CDR3, (2) a serine is at position [and] 97 in the L-CDR3, or (3) a threonine is at position 94 and a serine is at position 97 in [a] the L-CDR3 [are from a non-human anti-TAG-72 antibody],

wherein the humanized CC49 antibody retains binding affinity for TAG-72 and has reduced immunogenicity, when compared to a parental humanized CC49 antibody.

35. (Once amended) [A] The humanized [anti-TAG-72] antibody of claim 34, wherein the threonine is at position 94 in the L-CDR3 [comprising:

light chain Complementarity Determining Regions (L-CDRs), comprising L-CDR1, L-CDR2, and L-CDR3; and heavy chain Complementarity Determining Regions (H-CDRs), comprising H-CDR1, H-CDR2, and H-CDR3,

wherein residues at positions 31, 32, and 34 in H-CDR1 are from a non-human anti-TAG-72 antibody].

Please cancel claims 36 and 37

38. (Twice amended) A pharmaceutical composition [for treatment of cancer], comprising a therapeutically effective amount of the humanized antibody of claim 1 in a pharmaceutically acceptable carrier.

39. (Canceled) [A composition for detecting cancer cells, comprising the humanized antibody of claim 1.]

40. (Twice amended) A composition [for detecting cancer cells, comprising a [polypeptide capable of specifically binding TAG-72, said polypeptide] comprising a functional fragment of the humanized antibody of claim 1, wherein the functional fragment specifically binds TAG-72.

41. (Once amended) The composition of claim 40, wherein the [polypeptide comprises a] fragment [selected from the group consisting of] comprises an Fv, an Fab, [and] or an $F(ab')_2$.

42. (Once amended) A method for treating a cancer in a patient comprising:

administering a therapeutically effective amount of the humanized antibody of claim 1 to [a] the patient, thereby treating the cancer in the patient.

Please cancel claims 43-47.

Please add the following new claims:

48. (New) -- The humanized antibody of claim 2, wherein the human L-CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 7.

49. (New) The humanized antibody of claim 4, wherein the human L-CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 8.

50. (New) The humanized antibody of claim 6, wherein the human L-CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 7 and the human L-CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 8.

51. (New) The humanized antibody of claim 11, wherein a lysine at position 64 in the murine CC49 H-CDR2 is replaced with a glutamine.

52. (New) The humanized antibody of claim 11, wherein the amino acid at the corresponding position in the human monoclonal 21/28'CL antibody comprises an amino acid corresponding to position 12, 13, 14, or 16 of the amino acid sequence as set forth in SEQ ID NO: 11.

53. (New) The humanized antibody of claim 11, wherein the parental humanized CC49 antibody comprises three light chain hypervariable regions and three heavy chain hypervariable regions from the murine monoclonal CC49 antibody, a variable light chain framework from a human monoclonal LEN antibody, and a variable heavy chain framework from a human monoclonal 21/28'CL antibody.

54. (New) The humanized antibody of claim 15, wherein the human L-CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 7.

55. (New) The humanized antibody of claim 17, wherein the human L-CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 8.

56. (New) The humanized antibody of claim 19, wherein the human L-CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 7 and the human L-CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 8.

57. (New) The humanized antibody of claim 23, wherein the parental humanized CC49 antibody comprises three light chain hypervariable regions and three heavy chain hypervariable regions from the murine monoclonal CC49 antibody, a variable light chain framework from a human monoclonal LEN antibody, and a variable heavy chain framework from a human monoclonal 21/28'CL antibody.

58. (New) The humanized antibody of claim 24, wherein the amino acid at the corresponding position in the human monoclonal 21/28'CL antibody comprises amino acid 12, 13, 14, or 16, respectively, of an amino acid sequence as set forth in SEQ ID NO: 11.

59. (New) The humanized antibody of claim 24, wherein an asparagine at position 60 in the murine CC49 H-CDR2 is replaced with a serine.

60. (New) The humanized antibody of claim 24, wherein a glutamic acid at position 61 in the murine CC49 H-CDR2 is replaced with a glutamine.

61. (New) The humanized antibody of claim 24, wherein an arginine at position 62 in the murine CC49 H-CDR2 is replaced with a lysine.

62. (New) The humanized antibody of claim 24, wherein a lysine at position 64 in the murine CC49 H-CDR2 is replaced with a glutamine.

63. (New) The humanized antibody of claim 26, wherein the human L-CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 7.

64. (New) The humanized antibody of claim 28, wherein the human L-CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 8.

65. (New) The humanized antibody of claim 30, wherein the human L-CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 7 and the human L-CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 8.

66. (New) The humanized antibody of claim 34, wherein the serine is at position 97 in the L-CDR3.

67. (New) The humanized antibody of claim 34, wherein the threonine is at position 94 in the L-CDR3 and the serine is at position 97 in the L-CDR3.

68. (New) The humanized antibody of claim 11, wherein an asparagine at position 60 in the murine CC49 H-CDR2 is replaced with a serine, a glutamic acid at position 61 in the murine CC49 H-CDR2 is replaced with a glutamine, an arginine at position 62 in the murine CC49 H-CDR2 is replaced with a lysine, and a lysine at position 64 in the murine CC49 H-CDR2 is replaced with a glutamine.

69. (New) A kit comprising the humanized antibody of claim 1, a carrier or buffer, and instructions for using the humanized antibody.--